SYNTHESES OF SOME N-CARBOXYMETHYL DERIVATIVES OF 4,9-DIHYDRO-3-METHYL-4-OXO-1*H*-(2*H*)-PYRAZOLO[3,4-*b*]-QUINOLINE WITH ANTIVIRAL EFFECTS

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The paper describes the syntheses of 4,9-dihydro-9-carboxymethyl-1,3-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (*Ic*), 4,9-dihydro-9-carboxymethyl-2,3-dimethyl-4-oxo-2*H*-pyrazolo[3,4-*b*]-quinoline (*IIc*), 4,9-dihydro-1-carboxymethyl-3-methyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (*Id*), 4,9-dihydro-1-carboxymethyl-3,9-dimethyl-4-oxo-1*H*-pyrazolo [3,4-*b*] quinoline (*If*) and 4,9-dihydro-2-carboxymethyl-3,9-dimethyl-4-oxo-2*H*-pyrazolo[3,4-*b*]quinoline (*IIf*). The compounds were tested *in vivo* in mice for their efficacy against the virus A_2-Hongkong and the encephalomyocarditis virus.

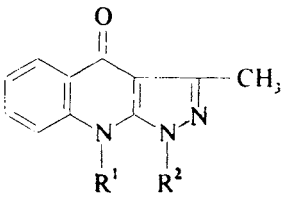
A number of tricyclic compounds administered to mice, perorally or parenterally, are known to induce the biosynthesis of interferon[1]. The most effective interferon inducers include acridine antimalarics Acranil[R] and quinacrine[2], and a similar derivative having the skeleton of pyrazolo[3,4-*b*]quinoline, referred to in the literature as BL-20803 (1,3-dimethyl-4-(3-dimethylaminopropylamino)-1*H*-pyrazolo[3,4-*b*]-quinoline dihydrochloride)[3]. An effective interferon inducer of a different type is sodium 9-oxo-9,10-dihydroacridine-10-yl acetate[4]. The interferon inducing activity of these compounds has incited us to syntheses of analogues of the latter with the pyrazolo[3,4-*b*]quinoline skeleton.

The presence of three atoms of nitrogen in this skeleton makes it possible to attach a carboxymethyl group to three different positions of the molecule. Thus we prepared compounds *Ib*–*If*, *IIb*, *IIc*, *IIe*, and *IIf*. The starting compounds *Ia*, *IIa*, and *IId* were obtained as described in the literature[5–7].

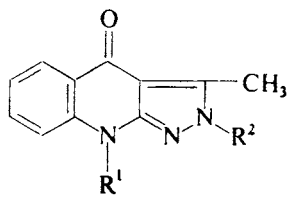
Alkylation of *Ia* with ethyl bromoacetate in acetone, in the presence of anhydrous potassium carbonate and potassium iodide, gave *Ib*. Alkaline hydrolysis of the latter afforded sodium salt of *Ic*, from which the free acid was obtained with the aid of cation exchanger Zerolite 225 (SRC 10) in the H-form. Alkylation of 4-chloro-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoline (*IIIa*) with ethyl bromoacetate in dimethyl sulphoxide, in the presence of powdered potassium hydroxide, yielded the chloro derivative *IIIb*. Under these conditions the rather reactive chlorine atom at the 4-position remained intact. Hydrolysis of *IIIb* by boiling in dilute hydrochloric acid produced

Id. This was alkylated, using two-fold molar amounts of methyl iodide and sodium hydride in dimethylformamide, to *Ie* which was then hydrolysed to the acid *If*.

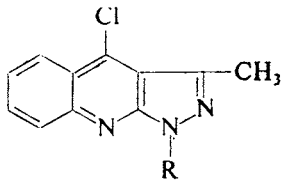
Alkylation of sodium salt of *IIa* with ethyl bromoacetate gave *IIb* which was hydrolysed to *IIc*. Similarly, alkylation of *IId* afforded *IIe* which was hydrolysed to *IIf*.



Ia; $R^1 = H$, $R^2 = CH_3$
Ib; $R^1 = CH_2COOC_2H_5$, $R^2 = CH_3$
Ic; $R^1 = CH_2COOH$, $R^2 = CH_3$
Id; $R^1 = H$, $R^2 = CH_2COOH$
Ie; $R^1 = CH_3$, $R^2 = CH_2COOCH_3$
If; $R^1 = CH_3$, $R^2 = CH_2COOH$



IIa; $R^1 = H$, $R^2 = CH_3$
IIb; $R^1 = CH_2COOC_2H_5$, $R^2 = CH_3$
IIc; $R^1 = CH_2COOH$, $R^2 = CH_3$
IId; $R^1 = CH_3$, $R^2 = H$
IIe; $R^1 = CH_3$, $R^2 = CH_2COOC_2H_5$
IIf; $R^1 = CH_3$, $R^2 = CH_2COOH$



IIIa, R = H
IIIb, R = $CH_2COOC_2H_5$

The compounds *Ib*–*If*, *IIb*, *IIc*, *IIe*, and *IIf* were tested *in vivo* for the effects against the influenza virus A2-Hongkong and the encephalomyocarditis (EMC) virus after peroral and subcutaneous administration to mice. The assay was described in the previous paper[5]. The standard used was 9-oxo-9,10-dihydroacridine-10-yl acetic, acid prepared by a described method[4]. *Ib* administered *s.c.* against 5 LD_{50} and 50 LD_{50} of the EMC virus extended the survival times by 52% and 100%, respectively; *Ic* administered *s.c.* against 5 and 50 LD_{50} of the EMC virus extended the survival times by 68% and 121 to 164%, respectively. The standard administered *s.c.* against 50 LD_{50} of the EMC virus extended the survival time by 117 to 157%. In the peroral administration, *Ib* also exhibited some efficacy against the A2-Hongkong virus, extending the survival time after 5 LD_{50} by 54%; in the case of *Ic* the survival time was extended by 42%. The standard proved quite ineffectual against the A2-Hongkong virus.

EXPERIMENTAL

The melting points were determined in an apparatus Mettler FP5, those exceeding 300°C were determined in the capillary on a copper block, and were not corrected. The IR spectra in the KBr pellet were measured employing an apparatus Perkin Elmer 577, the UV spectra in an apparatus Perkin Elmer 550 S. The ^{1}H NMR spectra were measured in an apparatus BS-487C (Tesla, Brno) 80 Hz. The standard was pentadeuterated 3-trimethylsilylpropionic acid (unless otherwise stated). The mass spectra were measured using apparatuses MCH 1320 and MAT 44 S.

9-Ethoxycarbonylmethyl-4,9-dihydro-1,3-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (*Ib*)

To a suspension of *Ia* (2·13 g, 10 mmol) in acetone (50 ml) were added anhydrous potassium carbonate (1·37 g), potassium iodide (0·33 g) and ethyl bromoacetate (1·67 g, 10 mmol). The mixture was stirred under reflux for 6 h. More potassium carbonate (anhydrous, 0·69 g) and ethyl bromoacetate (0·84 g, 5 mmol) were added and the mixture was refluxed for another 4 h. After cooling it was poured into water (200 ml), and the insoluble portion was collected on a filter, washed with water and crystallized from ethanol; yield 1·35 g (45%), m.p. 213·2–215·0°C. For $C_{16}H_{17}N_3O_3$ (299·3) calculated: 64·20% C, 5·72% H, 14·04% N; found: 64·24% C, 5·90% H, 14·35% N. IR spectrum (KBr): 1 735 (CO ester), 1 580 (CO quinolone), 1 615, 1 560 (C=C, C=N), 760 cm^{-1} (*o*-substituted aromate). UV spectrum (ethanol): λ_{max} 237 nm (log ε 4·66), 270 nm (3·76), 333 nm (3·86), λ_{infl} 210 nm, 280 nm, 340 nm. Mass spectrum, *m/z*: 299 (M^+). ^{1}H NMR spectrum (C^2HCl_3, tetramethylsilane): 8·30 (dd, J = 8·5 Hz, 1·5 Hz, 1 H, 5-H), 7·50 (bt, 1 H, 7-H), 7·20 (m, 1 H, 6-H), 6·98 (bd, 1 H, 8-H), 4·90 (s, 2 H, NCH_2), 4·30 (q, J = 7 Hz, 2 H, CH_2), 3·98 (s, 3 H, NCH_3), 2·58 (s, 3 H, CH_3), 1·31 (t, J = 7·0 Hz, 3 H, CH_2CH_3).

9-Carboxymethyl-4,9-dihydro-1,3-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (*Ic*)

A mixture of *Ib* (1·2 g, 4 mmol), 1·5M-NaOH (16 ml) and methanol (24 ml) was stirred 1 h at room temperature, passed through a column (40 g) of Zerolite 225 (SRC 10) in the H-form, pre-washed with 50% methanol. The column was washed with 50% methanol. The solution that had passed through the column was taken to dryness and the residue was recrystallized from methanol; yield 0·97 g (89%), m.p. 218·7–220·6°C. For $C_{14}H_{13}N_3O_3$ (271·3) calculated: 61·99% C, 4·83% H, 15·48% N; found: 61·51% C, 4·98% H, 15·74% N. IR spectrum (KBr): 1 700 (carboxyl CO), 1 620, 1 560 (C=N), 1 580 (quinolone CO), 750 cm^{-1} (*o*-substituted aromate). UV spectrum (ethanol): λ_{max} 241 nm (log ε 4·60), 337 nm (3·81), λ_{infl} 270 nm, 210 nm. ^{1}H NMR spectrum ($(C^2H_3)_2SO$): 8·25 (dd, J = 8·5 Hz, 1·5 Hz, 1 H, 5-H), 7·70 (bt, 1 H, 7-H), 7·50 (bd, J = 8·5 Hz, 1·5 Hz, 1 H, 8-H), 7·30 (bt, 1 H, 6-H), 5·30 (s, 2 H, CH_2), 4·05 (s, 3 H, NCH_3), 2·46 (s, 3 H, CH_3).

4-Chloro-1-ethoxycarbonylmethyl-3-methyl-1*H*-pyrazolo[3,4-*b*]quinoline (*IIIb*)

To a suspension of *IIIa* (2·17 g, 10 mmol) in dimethyl sulphoxide (25 ml) was added powdered potassium hydroxide (0·85 g) and the mixture was stirred 1 h at room temperature. Ethyl bromoacetate (1·84 g, 11 mmol) was added, whereby a solid precipitated. The mixture was diluted with dimethyl sulphoxide (25 ml), stirred 2 h at room temperature and poured into water. The insoluble portion was collected on a filter, washed with water and recrystallized from ethyl acetate; yield 2·25 g (74%), m.p. 140·7–141·6°C. For $C_{15}H_{14}ClN_3O_2$ (303·7) calculated: 59·38% C, 4·65% H, 11·67% Cl, 13·83% N; found: 59·28% C, 4·69% H, 11·62% Cl, 13·92% N.

1-Carboxymethyl-4,9-dihydro-3-methyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (*Id*)

A mixture of *IIIb* (4·6 g, 15 mmol) and 2M-HCl (50 ml) was stirred under reflux for 2 h. After cooling down the insoluble portion was collected on a filter, washed with water and recrystallized from ethanol; yield 3·3 g (83%), m.p. 328–331°C. For $C_{13}H_{11}N_3O_3$ (257·2) calculated: 60·70% C, 4·31% H, 16·33% N; found: 60·38% C, 4·56% H, 15·97% N.

1-Methoxycarbonylmethyl-4,9-dihydro-3,9-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (*Ie*)

To a suspension of *Id* (2·57 g, 10 mmol) in dimethylformamide (30 ml) was added 80% sodium hydride (0·75 g) and the mixture was stirred 1 h under nitrogen at room temperature. Methyl iodide (3·53 g, 25 mmol) was then added dropwise and the stirring was continued for another 4 h at room temperature. After an addition of water (30 ml), the stirred mixture was cooled to 5°C, the separated solid was collected on a filter, washed with water and recrystallized from methanol; yield 1·95 g (68%), m.p. 149·6–150·2°C. For $C_{15}H_{15}N_3O_3$ (285·3) calculated: 63·15% C, 5·30% H, 14·73% N; found: 63·42% C, 5·21% H, 14·59% N. ^{1}H NMR spectrum ($(C^2H_3)_2SO$): 8·20 (bd, 1 H, 5-H), 7·10–7·70 (m, 3 H, 6,7,8-H), 5·45 (s, 2 H, NCH_2), 3·85, 3·78 (s, 3 H each, NCH_3, $COOCH_3$), 2·52 (s, 3 H, CH_3).

1-Carboxymethyl-4,9-dihydro-3,9-dimethyl-4-oxo-1*H*-pyrazolo[3,4-*b*]quinoline (*If*)

This was obtained from *Ie*, adhering to the procedure for the preparation of *Ic*; yield 94%, m.p. 292·8–296·2°C. For $C_{14}H_{13}N_3O_3$ (271·3) calculated: 61·99% C, 4·83% H, 15·49% N; found: 61·58% C, 4·88% H, 15·58% N. UV spectrum (ethanol): λ_{max} 240 nm (log ε 4·64), 273 nm (3·73), 339 nm (3·86), λ_{infl} 345 nm.

9-Ethoxycarbonylmethyl-4,9-dihydro-2,3-dimethyl-4-oxo-2*H*-pyrazolo[3,4-*b*]quinoline (*IIb*)

80% Sodium hydride (0·5 g, 17 mmol) was added to a suspension of *IIa* (3·19 g, 15 mmol) in dimethylformamide (40 ml) and the mixture was stirred 1 h under nitrogen at room temperature. Following an addition of ethyl bromoacetate (2·75 g, 17 mmol), the stirring was continued for additional 2 h. After an addition of water (40 ml) the temperature of the mixture was lowered to 5°C; the separated solid was collected on a filter, washed with water and crystallized from ethanol; yield 3·8 g (85%), m.p. 210·6–211·7°C. For $C_{16}H_{17}N_3O_3$ (299·3) calculated: 64·20% C, 5·72% H, 14·04% N; found: 64·44% C, 5·61% H, 14·44% N. ^{1}H NMR spectrum (C^2HCl_3, tetramethylsilane): 8·30 (dd, J = 8·5 Hz, 1·5 Hz, 5-H), 7·45 (bt, 1 H, 7-H), 7·05 (bt, 1 H, 6-H), 6·92 (dd, J = 8·5 Hz, 1·5 Hz, 1 H, 8-H), 4·90 (s, 2 H, NCH_2), 4·11 (q, J = 7·0 Hz, 2 H, CH_2), 3·68 (s, 3 H, NCH_3), 2·62 (s, 3 H, CH_3), 1·18 (t, J = 7·0 Hz, 3 H, CH_2CH_3).

9-Carboxymethyl-4,9-dihydro-2,3-dimethyl-4-oxo-2*H*-pyrazolo[3,4-*b*]quinoline (*IIc*)

Analogously to the preparation of *Ic*, *IIc* was obtained from *IIb*; yield 96%, m.p. 213·3–213·6°C. For $C_{14}H_{13}N_3O_3$ (271·3) calculated: 61·99% C, 4·83% H, 15·48% N; found: 61·90% C, 4·79% H, 15·88% N. UV spectrum (ethanol): λ_{max} 239 nm (log ε 4·63), 285 nm (3·88), 369 nm (3·85), λ_{infl} 213 nm. ^{1}H NMR spectrum ($(C^2H_3)_2SO$): 8·20 (dd, J = 8·5 Hz, 1·5 Hz, 1 H, 5-H), 7·61 (bt, 1 H, 7-H), 7·35 (dd, J = 8·5 Hz, 1·5 Hz, 1 H, 8-H), 7·12 (bt, 1 H, 6-H), 5·00 (s, 2 H, CH_2), 3·78 (s, 3 H, NCH_3), 2·67 (s, 3 H, CH_3).

2-Ethoxycarbonylmethyl-4,9-dihydro-3,9-dimethyl-4-oxo-2*H*-pyrazolo[3,4-*b*]quinoline (*IIe*)

This was prepared from *IId* by the procedure for the preparation of *IIb*; yield 83%, m.p. 187·5 to 188·8°C. For $C_{16}H_{17}N_3O_3$ (299·3) calculated: 64·20% C, 5·72% H, 14·04% N; found: 64·18% C, 5·99 H, 13·76% N. UV spectrum (ethanol): λ_{max} 218 nm (log ε 4·30), 241 nm (4·70), 283 nm (4·00), 3·72 nm (3·89). ^{1}H NMR spectrum ($(C^2H_3)_2SO$, 80°C): 8·18 (dd, 1 H, 5-H), 7·52 (m, 1 H, 7-H), 7·40 (bd, 1 H, 8-H), 7·10 (m, 1 H, 6-H), 5·08 (s, 2 H, NCH_2), 4·18 (q, J = 7·0 Hz, 2 H, CH_2), 3·69 (s, 3 H, NCH_3), 1·21 (t, J = 7·0 Hz, 3 H, CH_2CH_2).

2-Carboxymethyl-4,9-dihydro-3,9-dimethyl-4-oxo-2*H*-pyrazolo[3,4-*b*]quinoline (*IIf*)

This was obtained from *IIe*, adhering to the procedure for the preparation of *Ic*; yield 88%, m.p. 281·1—283·9°. For $C_{14}H_{13}N_3O_3$ (271·3) calculated: 61·99% C, 4·83% H, 15·48% N; found: 61·70% C, 5·12% H, 15·26% N. UV spectrum (ethanol): λ_{max} 242 nm (log ε 4·68), 286 nm (3·90), 375 nm (3·85), λ_{infl} 255 nm.

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